

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of claims:

1. (Currently Amended) A method for treating diabetes, ~~insulin resistance, obesity, hyperglycemia, hyperinsulinemia, or elevated fatty acids, glycerol, or atherosclerosis~~ which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of an aP2 inhibitor, wherein the aP2 inhibitor includes an oxazole or analogous ring.

2. (Original) The method as defined in Claim 1 wherein the aP2 inhibitor binds to the aP2 protein and inhibits its function and/or its ability to bind free fatty acids.

- 3-4. (Cancelled)

5. (Currently Amended) The method as defined in Claim 1 ~~3~~ where said aP2 inhibitor contains ~~an additional~~ a substituent which binds within and/or interacts with a discrete pocket within the aP2 protein defined by the amino acid residues designated Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2 (SEQ ID NO: 1).

6. (Currently Amended) The method as defined in Claim 5 wherein said ~~additional~~ substituent in said aP2 inhibitor is hydrophobic in nature.

7. (Original) The method as defined in Claim 5 in which the through space distance from the hydrogen bond donor/acceptor group and the additional substituent group in said aP2 inhibitor is within the distance of about 7 to about 15 Angstroms.

8. (Original) The method as defined in Claim 1 wherein Type II diabetes is treated.

9. (Original) The method as defined in Claim 1 wherein the aP2 inhibitor is employed in the form of a pharmaceutically acceptable salt thereof or a prodrug ester thereof.

10. (Cancelled)

11. (Currently Amended) The method as defined in Claim 1 ~~10~~ wherein the aP2 inhibitor is a substituted benzoyl or biphenyl-2-oxazole-alkanoic acid derivative, an oxazole derivative, a 2-thio-4,5-diphenyloxazole S-derivative, a phenyl-heterocyclic oxazole derivative, a diaryloxazole derivative, a 4,5-diphenyloxazole derivative, an oxazole carboxylic acid derivative, a phenyloxazolyloxazole derivative, or a 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acid derivative.

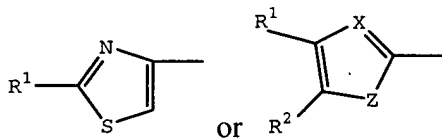
12-13. (Cancelled)

14. (Currently Amended) The method as defined in Claim 1 ~~10~~ wherein the aP2 inhibitor is (I) a substituted benzoylbenzene or biphenyl alkanoic acid derivative having the structure:

I $A(CH_2)_nO-B$

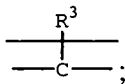
wherein

A is a group having the formula

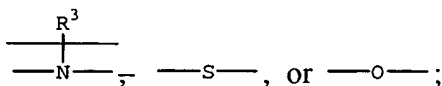
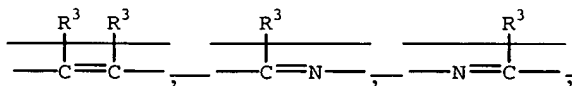


wherein

X is -N- or



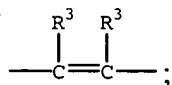
Z is



R^1 is hydrogen, lower alkyl or phenyl;

R^2 is hydrogen or lower alkyl; or

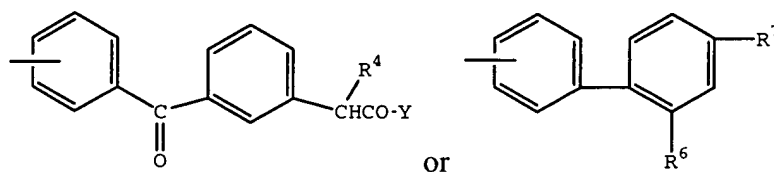
R^1 and R^2 taken together form a benzene ring, with the proviso that when X is -N-, Z is other than



~~R^3 is hydrogen or lower alkyl;~~

n is 1-2;

B is



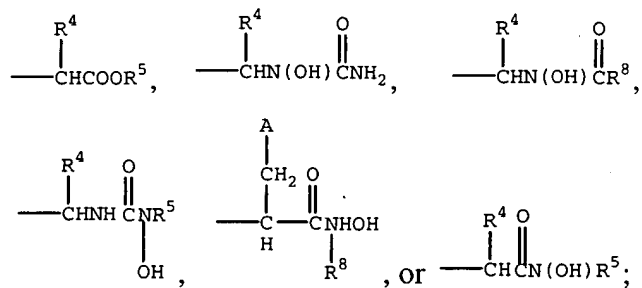
wherein

Y is OR^5 or $N(OH)R^8$;

R^4 and R^5 are each, independently, hydrogen or lower alkyl;

R^6 is hydrogen, halo or nitro;

R^7 is



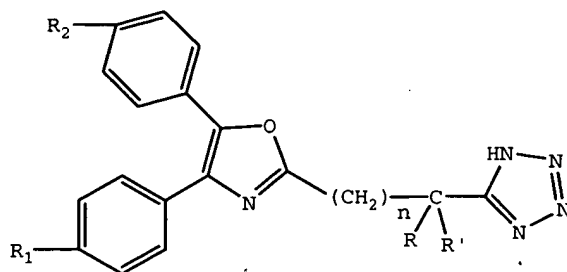
R^8 is lower alkyl;

m is 0-3;

or a pharmacologically acceptable salts thereof;

(II) oxazole derivatives which have the structure

II



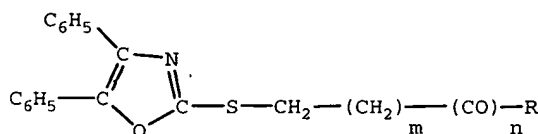
in which;

R and R' are identical or different and represent a hydrogen atom or an alkyl radical containing 1 or 2 carbon atoms,

R₁ and R₂ are identical or different and represent hydrogen or halogen atoms or alkyloxy radicals in which the alkyl portion contains 1 to 4 carbon atoms in a straight or branched chain, and n equals 3 to 6, as well to their salts;

(III) 2-thiol-4,5-diphenyloxazole S-derivatives which have the structure

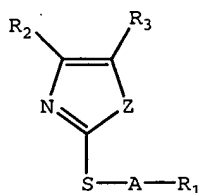
III



wherein m is 0, 1 or 2, n is 1 and R represents hydroxy, alkoxy or amino, and pharmaceutically acceptable addition salts thereof;

(IV)azole derivatives of the structure

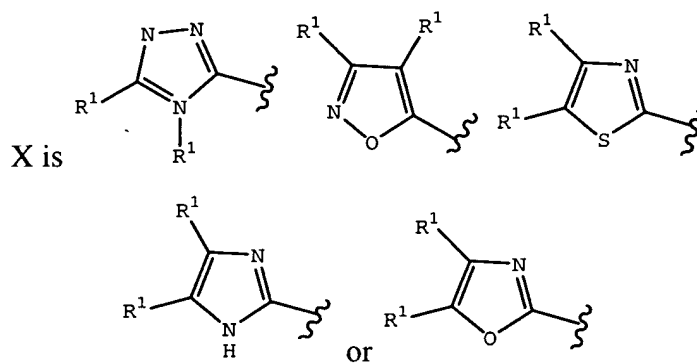
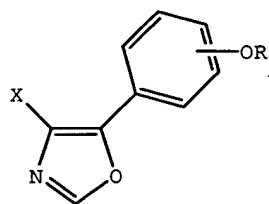
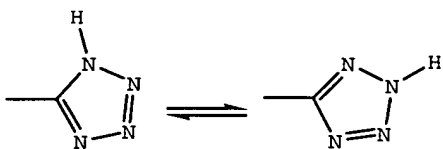
IV



wherein R₁ is carboxyl, esterified carboxyl or other functionally modified carboxyl group; R₂ and R₃ each are aryl of up to 10 carbon atoms; A is C_nH_{2n} in which n is an integer from 1 to 10, inclusive; and Z is O or S, and physiologically acceptable salts thereof;

(V) phenyl-heterocyclic oxazole derivatives which have the structure

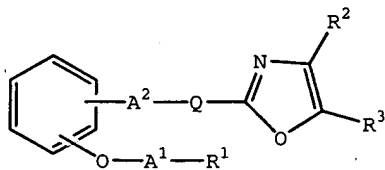
V

R is CH_2R^2 ; R^1 is Ph or Th; R^2 is CO_2R^3 ; and R^3 is H, or C_1 - C_4 lower alkyl;

or pharmaceutically acceptable salt thereof;

(VI) diaryloxazole derivatives having the structure

VI

wherein R^1 is carboxy or protected carboxy,

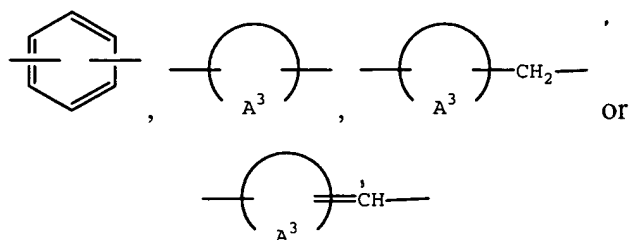
R^2 is aryl,

R^3 is aryl,

A^1 is lower alkylene,

A^2 is bond or lower alkylene and

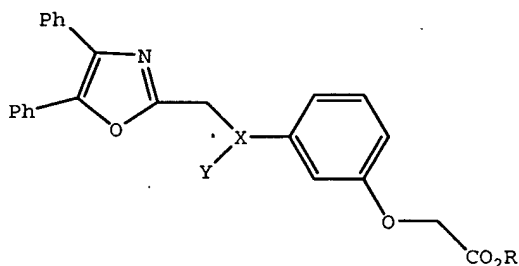
-Q- is



(in which is cyclo (lower)alkane or cycle(lower)alkene,

each of which may have suitable substituent(s));

(VII) 4,5-diphenyloxazole derivatives having the structure VIIA



wherein

R is H or C₁-C₅ lower alkyl,

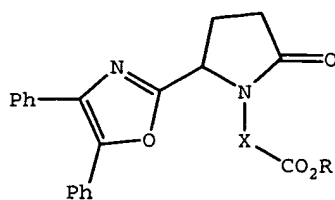
X is N or CH,

Y is H or CO₂R¹, or COR², provided that when X is CH, Y is not H,

R¹ is C₁-C₅ lower alkyl, or phenylmethyl, and

R² is C₁-C₅ alkyl; or

VIIB



wherein

R is H or C₁-C₅ lower alkyl,

X is (CH₂)_n or para or meta substituted phenyl wherein the substituent is OR²,

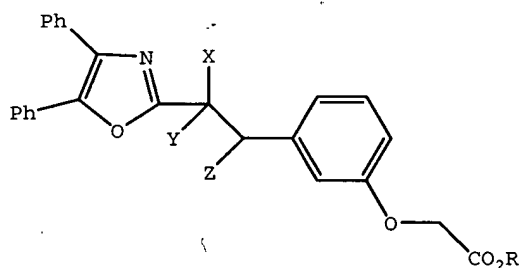
R² is C₁-C₅ alkyl, and

n is an integer of 4 to 8,

and pharmaceutically acceptable salts thereof;

(VIII) oxazole carboxylic acid derivatives having the structure

VIII



wherein

Y and Z are independently hydrogen or together form a bond;

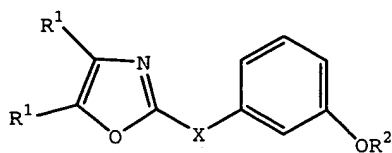
X is CN, CO₂R¹ or CONR²R³;

R and R¹ are independently or together H, Na, or
C₁-C₅ lower alkyl;

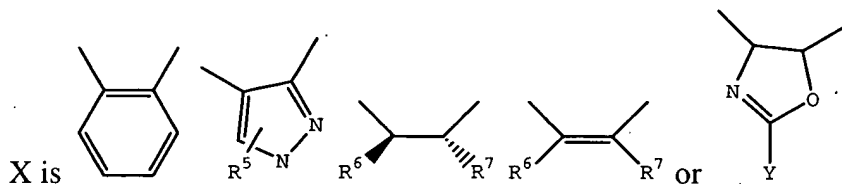
R² and R³ are independently or together H, or C₁-C₅ lower alkyl;
or alkali metal salt thereof;

(IX) phenyloxazolyloxazole derivatives having the structure

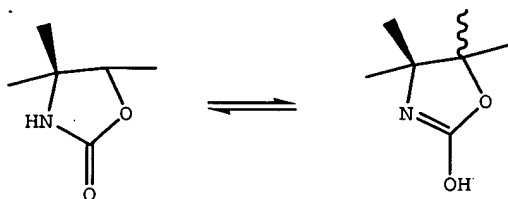
IX



wherein



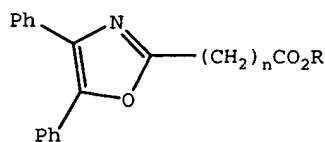
Y is CH₃, Ph, or OH, provided that when Y is OH, the compound exists in the keto-enol tautomerism form

R¹ is Ph or Th;R² is CH₂R³;R³ is CO₂R⁴;R⁴ is H or C₁-C₅ lower alkyl;R⁵ is H or CH₃; R⁶ is OHCHN or H₂N; andR⁷ is H or OH;

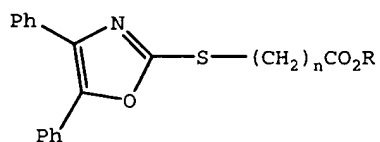
or pharmaceutically acceptable salt thereof;

(X) 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acids and esters having the structure

XA

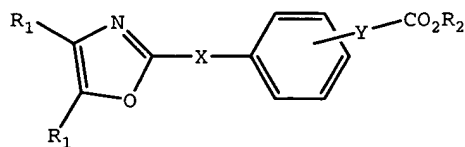


XB



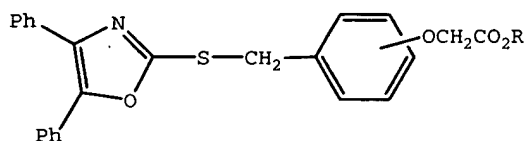
(wherein n is 7-9 and R is hydrogen or lower alkyl; or when R is hydrogen, the alkali metal salt thereof),

XC



or

XD



wherein

R₁ is phenyl or thienyl;

R₂ is hydrogen, lower alkyl or together with CO₂ is tetrazol-1-yl;

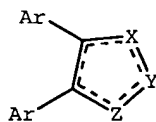
X is a divalent connecting group selected from the group consisting of CH₂CH₂, CH=CH, and CH₂O;

Y is a divalent connecting group attached to the 3- or 4-phenyl position selected from the group consisting of OCH₂, CH₂CH₂ and CH=CH,

or when R₂ is hydrogen, an alkali metal salt thereof;

(XI) substituted 4,5-diaryl heterocycles having the formula

XI



in which

each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;

X is nitrogen or CR¹;

Y is ~~nitrogen~~, $N(CH_2)_nA$ or $C(CH_2)_nA$;

Z is ~~nitrogen~~, oxygen or $N(CH_2)_nA$, and the dotted line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;

R^1 is hydrogen, C_1 -4alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

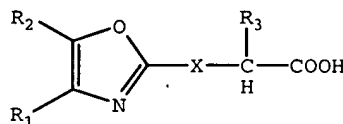
n is 4 to 12; and

A is CO_2H or a group hydrolysable to CO_2H ,

5-tetrazolyl, SO_3H , $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_1 -4alkyl, or a pharmaceutically acceptable salt thereof;

(XII) compounds which have the structure

XII



Where X is O or S;

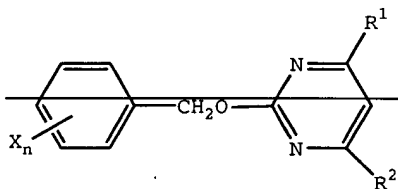
R_1 is H, phenyl or phenyl substituted with F, Cl or Br or alkoxy,

R_2 is H, alkyl, phenyl or phenyl substituted with F, Cl or Br or alkoxy, and

R_3 is H or alkyl;

~~(XIII) 2-benzylloxypyrimidine derivatives having the following structure~~

~~XIII~~



wherein

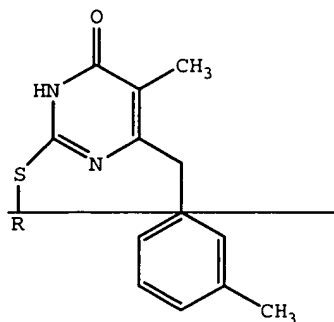
~~R^1 and R^2 are each independently H, a halogen, hydroxyl, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_5 alkenyl, C_3 - C_5 alkynyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_3 - C_5 alkenyloxy, C_3 - C_5 alkynyloxy, C_1 - C_4 alkylthio, or phenyl, with the proviso that at least one of R^1 and R^2 must be hydroxyl;~~

~~n is an integer of 0 to 5; and~~

each X which may be identical or different if n is greater than 1, is a halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₇-C₉ aralkyloxy, phenyl, hydroxymethyl, hydroxycarbonyl, C₁-C₄ alkoxycarbonyl, or nitro;

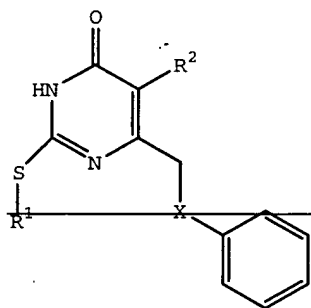
(XIV) dihydro(alkylthio) (naphthylmethyl) oxypyrimidines which have the structures

XIVA



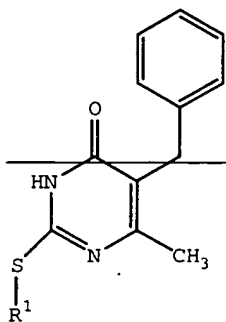
3a R=sec-butyl
3b R=cyclopentyl
3c R=cyclohexyl

XIVB

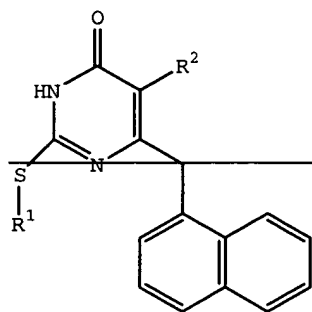


5 X=CH₂
6 X=O
7 X=S

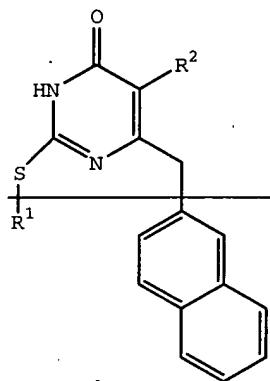
XIVC



—XIVD



—XIVE

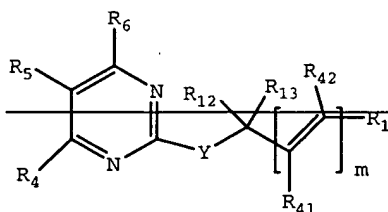


R^1 = sec butyl, cyclopentyl, cyclohexyl;

R^2 = H, CH₃, including tautomers of the above;

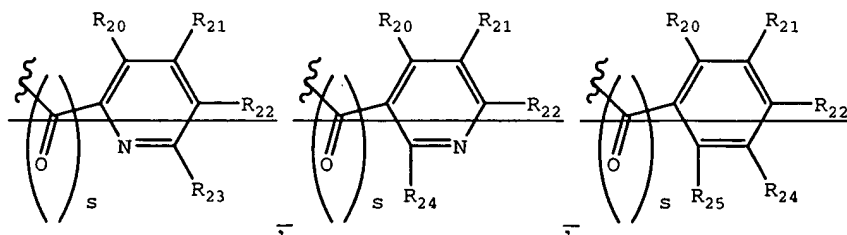
—(XVI) α -substituted pyrimidine thioalkyl and alkylether compounds which have the structure

—XVI



where m is 0 or 1;

— R^1 is selected from CO_2R_{53} , $\text{CONR}_{54}\text{R}_{55}$;



where s is 0 or 1, and R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, and R₂₅ are the same or different and are selected from H, C₁-C₆-alkyl, C₁-C₆-alkenyl, C₁-C₆-alkoxy, C₁-C₆-alkylthio, C₃-C₈-cycloalkyl, CF₃, NO₂, halo, OH, CN, phenyl, phenylthio, styryl, CO₂(R₃₁), CON(R₃₁)(R₃₂), CO(R₃₁), (CH₂)_nN(R₃₁)(R₃₂), C(OH)(R₃₁)(R₃₃), (CH₂)_nN(R₃₁)(CO(R₃₃)), (CH₂)_nN(R₃₁)(SO₂(R₃₃)), or where R₂₀ and R₂₁, or R₂₁ and R₂₂, or R₂₂ and R₂₃ are taken together to form a five or six membered saturated or unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C₁-C₆-alkyl, C₁-C₆-alkoxy, OH, CH₂OH, (CH₂)_nN(R₃₁)(R₃₂), C₃-C₈-cycloalkyl, CF₃, halo, CO₂(R₃₁), CON(R₃₁)(R₃₂), CO(R₃₁), (CH₂)_nN(R₃₁)(CO(R₃₃)), (CH₂)_nN(R₃₁)(SO₂(R₃₃)), CN, CH₂CF₃ or CH(CF₃)₂, or phenyl and the saturated ring may be optionally substituted with 1, 2 or 3, C₁-C₆-alkyl, C₁-C₆-alkoxy, OH, CH₂OH or (CH₂)_nN(R₃₁)(R₃₂) or one oxo (=O);

_____ where n is 0-3 and R₃₁, R₃₂ and R₃₃ are the same or different and are selected from

_____ H,

_____ C₁-C₆-alkyl,

_____ phenyl optionally substituted with 1, 2 or 3 halo, C₁-C₆-alkyl, C₁-C₆-alkoxy, CF₃, OH or CN,

_____ or where R₃₁ and R₃₂ taken together with the attached nitrogen to form a ring selected from pyrrolidinyl, piperidinyl, 4-morpholinyl, 4-thiomorpholinyl, 4-piperazinyl, 4-(1-C₁-C₆-alkyl)piperazinyl, or a member selected from

_____ 1-cyclohexenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-imidazolyl, 4-imidazolyl, 2-benzothiazolyl, 2-benzoxazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 5-methyl-3-isoxazolyl, 5-phenyl-3-isoxazolyl, 4-thiazolyl, 3-methyl-2-pyrazinyl, 5-methyl-2-pyrazinyl, 6-methyl-2-pyrazinyl, 5-chloro-2-thienyl, 3-furyl, benzofuran-2-yl, benzothien-2-yl, 2H-1-benzopyran-3-yl, 2,3-dihydrobenzopyran-5-yl, 1-methylimidazol-2-yl, quinoxalin-2-yl, piperon-5-yl, 4,7-dichlorobenzoxazol-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, 2,4-dimethylpyrimidin-6-yl, 2-methylpyrimidin-4-yl, 4-methylpyrimidin-6-yl, 6-chloropiperon-5-yl, 5-chloroimidazol[1,2-a]pyridin-2-yl, 1-H-inden-3-yl, 1-H-2-methyl-inden-2-yl, 3,4-dihydronaphth-1-yl, 5-4-isopropenylcyclohexen-1-yl or 4-dihydronaphth-2-yl;

_____ where R₅₃ is selected from H, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, phenyl (optionally substituted with 1, 2, or 3 halo, C₁-C₆-alkyl, C₁-C₆-alkoxy, CF₃, OH, CN), or a five or six membered unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring

may be optionally substituted with ~~H, C₁-C₆ alkyl, C₁-C₆ alkoxy, OH, CH₂OH, or (CH₂)_n-N(R₃₁)(R₃₂);~~

~~where R₅₄ and R₅₅ being the same or different are selected from H, C₁-C₆ alkyl, allyl, or phenyl (optionally substituted with 1, 2 or 3 halo, C₁-C₆ alkyl, C₁-C₆ alkoxy or CF₃), or taken together with the attached nitrogen to form a ring selected from pyrrolidinyl, piperidinyl, 4-morpholinyl, 4-thiomorpholinyl, 4-piperazinyl, 4-(1-C₁-C₆alkyl)piperazinyl;~~

~~R₄₁ and R₄₂, being the same or different, are selected from H and C₁-C₄ alkyl;~~

~~R₁₂ is selected from H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, CN, C(O)NH₂, C(O)N(C₁-C₆alkyl)(C₁-C₆alkyl), CO₂H, CO₂(C₁-C₆alkyl), CH₂OH, CH₂NH₂ or CF₃;~~

~~R₁₃ is selected from H, C₁-C₆ alkyl or CF₃;~~

~~Y is selected from S, S(O), S(O)₂, or O;~~

~~R₄ is OH;~~

~~R₅ is selected H, C₂H₄OH, C₂H₄-O-TBDMS, halo, C₃-C₆ cycloalkyl, C₁-C₃ alkoxy, CH₂CH₂Cl or C₁-C₄ alkyl, with the proviso that R₅ is not isobutyl;~~

~~or, when R₆ is hydroxyl, R₄ and R₅ are taken together to form a five or six membered saturated or unsaturated ring which together with the pyrimidine ring form the group consisting of 7H-pyrrolo[2,3-d]pyrimidine, 5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidine, furo[2,3-d]pyrimidine, 5,6-dihydro-furo[2,3-d]pyrimidine, thieno[2,3-d]pyrimidine, 5,6-dihydro-thieno[2,3-d]pyrimidine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-purine, pyrimido[4,5-d]pyrimidine, pteridine, pyrido[2,3-d]pyrimidine, or quinazoline, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C₁-C₆ alkyl, C₁-C₆ alkoxy, OH, CH₂OH, or (CH₂)_n-N(R₃₁)(R₃₂), C₃-C₈ cycloalkyl, CF₃, halo, CO₂(R₃₁), CON(R₃₁)(R₃₂), CO(R₃₁), (CH₂)_n-N(R₃₁)(CO(R₃₃)), (CH₂)_n-N(R₃₁)(SO₂(R₃₃)), and the saturated ring may be optionally substituted with 1, 2 or 3, C₁-C₆ alkyl, C₁-C₆ alkoxy, OH, CH₂OH, or (CH₂)_n-N(R₃₁)(R₃₂) or one oxo (=O); and~~

~~R₆ is selected from H, OH, halo, CN, CF₃, CO₂(R₆₁), C(O)R₆₁ or C(O)N(R₆₁)(R₆₂) where R₆₁ and R₆₂ are the same or different and are selected from~~

~~H,~~

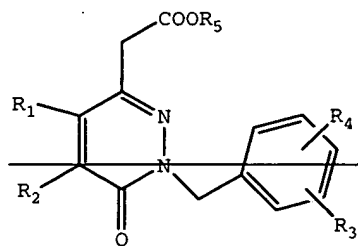
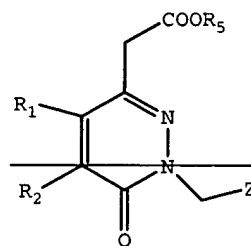
~~C₁-C₆ alkyl,~~

~~phenyl optionally substituted with 1, 2 or 3 halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, CN,~~

~~or where R₆₁ and R₆₂ taken together with the attached nitrogen to form a ring selected from pyrrolidinyl, piperidinyl, 4-morpholinyl, 4-thiomorpholinyl, 4-piperazinyl, or 4-(C₁-C₆ alkyl)piperazinyl;~~

~~pharmaceutically acceptable salts, hydrates, N-oxides and solvates thereof;~~

~~(XVII) compounds which have the structure~~

~~XVIIA~~~~XVIIIB~~

where R_1 and R_2 are H, alkyl, aryl or arylalkyl, where the alkyl can include as substituents halogen, CF_3 , CH_3O , CH_3S , NO_2 , or R_1 and R_2 with the carbons to which they are attached can form methylenedioxy, or

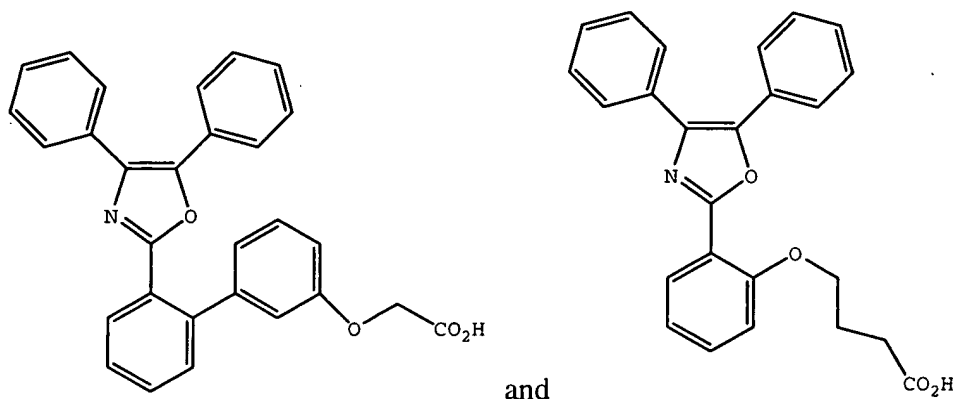
——— R_1 and R_2 can form a C3-C7 non-aromatic ring, or a heterocycle which can be pyridine, pyrazine, pyrimidine, pyridazine, indol, or pyrazole, or an oxygen-containing heterocycle which can be pyran or furan, or a sulfur-containing heterocycle which can be thiopyran, or thiophene; the heterocycles being optionally substituted with halogen or alkyl,

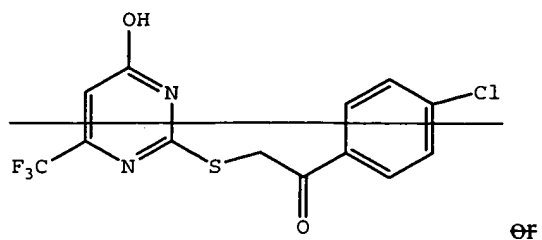
——— R_3 and R_4 are H, alkyl, halogen, CF_3 , CH_3O , CH_3S or NO_2 or R_3 and R_4 with the carbons to which they are attached can form a methylenedioxy group,

——— R_5 is H, and

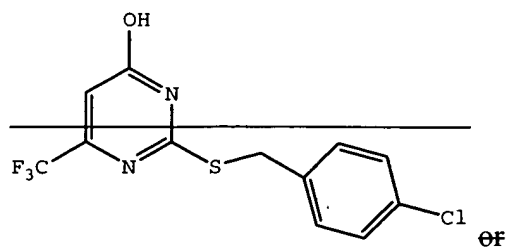
——— Z is a heterocycle which can be pyridine, thiazole, benzothiazole, benzimidazole or quinoline, which Z group can optionally be substituted with halogen or alkyl.

15. (Currently Amended) The method as defined in Claim 1 wherein the aP2 inhibitor has the structure

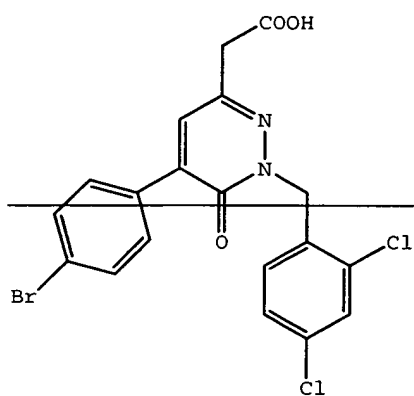




OF



OF



16-20. (Cancelled)